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10/816,768	04/02/2004	Hermann Oppermann	STK-075 CON	3980
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ROPE & GRAY LLP			LI, RUIXIANG	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

**Office Action Summary**

Application No.

10/816,768

Applicant(s)

OPPERMANN ET AL.

Examiner

Ruixiang Li

Art Unit

1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 27 June 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 1-5 and 10-19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 6-9, 20 and 21 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 04/02/2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 02/09/2005
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- ☐ Notice of Informal Patent Application
- ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election with traverse of Group IX in the reply filed on 03/07/2007 is acknowledged. Applicants also elected species OP-1 in the reply filed on 06/27/2007. The traversal is on the ground(s) that a search for groups IX is co-extensive with that group X and the two searches could be carried out simultaneously and that there would be no serious burden on the examiner if IX and X are examined together. This is found to be persuasive. Groups IX and X will be considered together.

The requirement is made FINAL.

2. Applicants' preliminary amendment filed upon 07/18/2005 has been entered in full. Claims 1-21 are pending. Claims 6-9, 20, and 21 are currently under consideration. All other claims are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

### ***Information Disclosure Statement***

3. The information disclosure statement filed on 02/09/2005 has been considered by the examiner.

### ***Drawings***

4. The drawings filed on 04/02/2004 are accepted by the examiner.

### ***Sequence Compliance***

5. This application contains sequence disclosures that are encompassed by the definitions for amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because not all the amino acid sequences present in the specification (see, e.g., pages 44 and 45) and drawings (see, e.g., Figs. 4-7) have been identified with a SEQ ID NO.

All the amino acid sequences appearing in the specification and drawings must be identified by a sequence identifier in accordance with 37 C.F.R. 1.821(d). Sequence identifiers for sequence appearing in the drawings may appear in the Brief Description of the Drawings. Applicants must provide appropriate amendments to the specification or drawings inserting the required identifiers. If the amendments are extensive then a substitute specification may be required.

### ***Objection to the Specification***

6. The disclosure is objected to because of the following informalities: there are numerous blank spaces (see, e.g., pages 1 and 76).

Appropriate correction is required.

### ***Claim Rejections—35 USC § 112, 1<sup>st</sup> paragraph***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 6-9, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 6-9, 20, and 21 are drawn to a latent TGF- $\beta$  family member fusion protein competent to refold under suitable refolding conditions, comprising a TGF- $\beta$  family protein C-terminal seven cysteine domain and a cleavable sequence operably linked to said C-terminal domain wherein said leader sequence inhibits the biological activity associated with said C-terminal domain, wherein said C-terminal domain becomes active upon cleavage of a part or all of said leader sequence. The claims are drawn to a genus of latent TGF- $\beta$  family member fusion proteins comprising a cleavable leader sequence linked to a TGF- $\beta$  family protein C-terminal domain. Thus, the claims encompass a genus of cleavable sequences operably linked to a genus of TGF- $\beta$  family protein C-terminal domains. The claims do not

require that the cleavable leader sequences possess any particular conserved structure nor other disclosed distinguishing feature.

The specification discloses a modified OP-1 comprising N-terminal decapeptide collagen binding site inserted upstream of the seven-cystein domain (see Fig. 7A) and stated that such a modified OP-1 can be delivered in an inactive form to a desired tissue locus and cleaved at the locus to produce an active morphoén (page 79, the 2<sup>nd</sup> paragraph). However, there is no actual showing that such a N-terminal leader sequence as recited in the claims is removed under endogenous conditions in vivo at the target conditions and that the C-terminal domain becomes active upon cleavage of a part or all of said leader sequence. Furthermore, there is no description of the structural features of a leader sequence as recited in the claims. There is no description regarding how to choose a leader sequence, such as one from another TGF- $\beta$  family protein, to be used as a leader sequence that inhibits the biological activity associated with a TGF- $\beta$  family protein C-terminal domain.

A description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). While disclosing a modified OP-1 comprising N-terminal decapeptide collagen binding site inserted upstream of the seven-cystein domain (see Fig. 7A), the instant

structural features of the genus of the recited leader sequences. The prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the genus of leader sequences encompassed by the instant claims.

Due to the breadth of the genus of recited leader sequences and lack of the definitive structural features of the genus, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus of leader sequences and thus the instantly claimed latent TGF- $\beta$  family member fusion proteins.

***Claim Rejections—35 USC § 112, 2<sup>nd</sup> paragraph***

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 6-9, 20, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is indefinite because it recites "refold under suitable refolding conditions". Since the specification fails to define the conditions unambiguously, the claim is indefinite.

Claim 7 recites "wherein a tissue-targeting domain is embedded within said cleavable lead sequence", which contradicts to another limitation "whereby cleavage of the leader sequence will not cleave said tissue-targeting domain from said C-terminal domain". If a tissue-targeting domain is embedded within a cleavable lead

sequence, the tissue-targeting domain would necessarily be cleaved from said C-terminal domain when the leader sequence is cleaved off.

Claims 8, 9, 20, and 21 are rejected as dependent claims from claim 6.

***Claim Rejections—35 U.S.C. §102 (e)***

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claim 6 is rejected under 35 U.S.C. 102(b) as being unpatentable over WO 91/05565 (2 May 1991).

WO 91/05565 teaches a fusion protein comprising a leader sequence and C-terminal domain (Fig. 2A and 2B, Abstract, pages 20 and 21). The leader sequence can be cleaved at the Asp-Pro-site in the hinge region with dilute acid, or at the Asn-Gly site with hydroxylamine (page 21, 2<sup>nd</sup> paragraph of page 21), and the C-terminal domain becomes active after refolding (the 3<sup>rd</sup> paragraph of page 2). Thus, the teachings of WO 91/05565 meet the limitations of claim 6.

***Claim Objections***

13. Claims 6-9 are objected to because they recite non-elected subject matter (TGF- $\beta$  family proteins). Appropriate correction is required.



**Conclusion**

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

*Ruixiang Li*

Ruixiang Li, Ph.D.  
Primary Examiner  
September 11, 2007

RUIXIANG LI, PH.D.  
PRIMARY EXAMINER